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NEWER METHODS OF REDUCTION*

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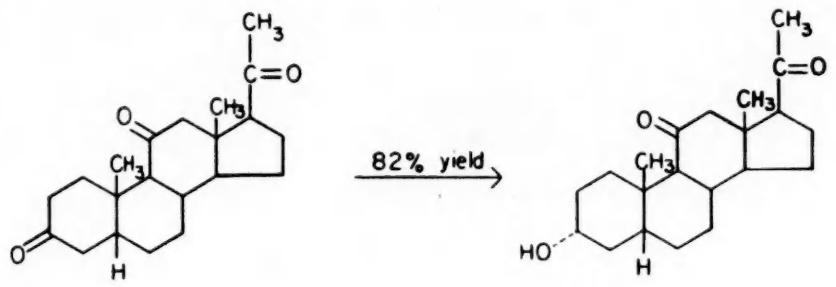
An impressive array of newer methods for the reduction of organic compounds has been developed within the past few years. These methods—chemical, catalytic, electrolytic—have proved invaluable in synthesizing many new compounds, particularly among the steroids, and a survey of the most important of the procedures is well justified. Some of these are new applications of known reducing agents.

Chemical Reductions

Metal Hydrides—A recent review (1) describes the extensive application of many metal hydrides ($LiAlH_4$, $Mg(AlH_4)_2$, $NaAlH_4$, $LiBH_4$, $NaBH_4$, KBH_4, $Ca(BH_4)_2$, $Na(OCH_3)_3BH$, and $LiGaH_4$) to the reduction of compounds containing oxygen, nitrogen, sulfur, and halogen. The selectivity of some of these reagents for particular groups in polyfunctional molecules makes them particularly useful. An excellent monograph by Gaylord (2) covers all the pertinent literature references up to 1953.

Sodium borohydride, $NaBH_4$, is an especially versatile reagent because it can be used in aqueous and other polar solvents, such as methanol, dioxane, tetrahydrofuran, and dimethyl ether of diethylene glycol ("diglyme"). In pyridine, it was used to reduce selectively the 3-keto group of steroids, as in the preparation (3) of pregnane-3α-ol-11,20-dione, a cortisone intermediate,



Brown (4) found that addition of a promoter, e. g., $AlCl_3$, would readily catalyze sodium borohydride reduction of esters, lactones, and carboxylic acids to alcohols.

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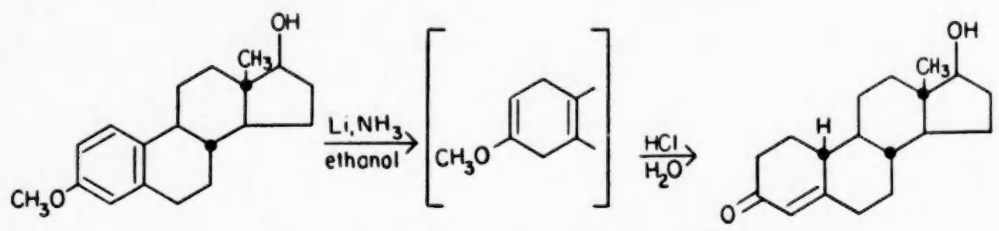
Lithium tributoxyaluminohydride, $Li(BuO)_3AlH$, was discovered (5) to be an effective reagent for converting acid chlorides to aldehydes. Diisobutylaluminohydride, $(C_4H_9)_2AlH$, was shown (6) to reduce 3-hexyne stereospecifically to *cis*-3-hexene; diborane, B_2H_6, was reported (7) to be a selective, acid type of reducing agent for aldehydes, ketones, nitriles, lactones, and carboxylic acids.

Metal–Liquid Ammonia Combinations—Various combinations of metals (sodium, potassium, or lithium) with liquid ammonia have proved to be versatile reducing agents. Wilds and Nelson (8) observed that lithium was more effective than either sodium or potassium for the Birch reduction of certain insoluble and unreactive phenolic ethers. Addition of ethanol at a later stage in the reaction was essential in their procedure. Their work resulted in a facile synthesis (70-77% yield) of 19-nortestosterone from estradiol methyl ether.



Dots denote the angular positions where the substituents project on the same side of the steroid molecule.

The Wilds and Nelson modification was also used to good advantage for conversion of the aromatic nucleus in a hydrochrysene phenol ether to its dihydro derivatives (9). Johnson (10) observed that a combination of potassium, liquid ammonia, and ethanol was effective for the stereoselective reduction (81% yield) of the 4b, 10b double bond in a tetracyclic phenol ether without attacking the aromatic nucleus.

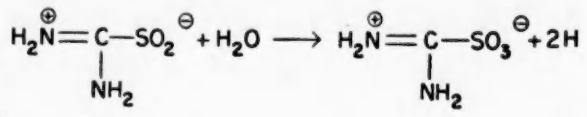
Phosphoric esters of phenols, $ArOP(O)(OC_2H_5)_2$, were converted (11) to hydrocarbons, ArH, in 60-93% yields by either sodium or lithium in liquid ammonia.

Lithium–Amines—Lithium in ethylamine is considered a more powerful reducing system (12) than lithium in ammonia, a property which can be attributed to increasing basicity of the solvent, ethylamine. This metal–amine combination, at −78° C., is a useful tool because it offers a unique method for leaving one unreduced bond in a ring. Thus, naphthalene was converted to 9,10-octalin, and ethylbenzene and acetophenone were reduced to 1-ethylcyclohexene and 1-(1-cyclohexenyl-ethanol), respectively. Lithium–ethylamine can also effect *trans*- reduction of acetylenes to olefins, e.g., 3-octyne and 5-decyne were converted to 3-octene and 5-decene in 50-55% yields.

An even more powerful reducing system was recently discovered by Reggel (13), who substituted ethylenediamine for ethylamine. This method reduced aromatic rings to cycloparaffins, acetylenes and olefins to alkanes, and ketones to alcohols.

Thiourea Dioxide—Thiourea dioxide, $H_2\overset{\oplus}{N}=C(NH_2)-SO_2^{\ominus}$, also known as aminoiminomethane sulfinic acid, is a very active reducing agent that will convert nitro, azoxy, azo, and hydrazo compounds to amines, quinones to hydroquinones, and

dyes to leuco bases (14). It will not attack ketones or α-diketones and can be utilized in water, pyridine, or dimethylformamide. Its reducing action is based on the ease of its oxidation to a sulfonic acid:

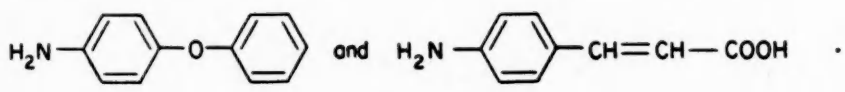


Zinc–Copper Couple—The zinc–copper couple was found (15) to be selective and stereospecific in reducing acetylenes to *cis*-olefins.

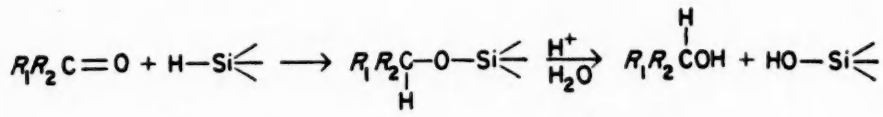
Hydrazine Hydrate—Hydrazine hydrate, $NH_2NH_2 \cdot H_2O$, alone and with palladium or Raney nickel, has been developed as a markedly effective reducing agent. Oleic acid was converted to stearic acid (93% yield) by the sole action of hydrazine hydrate (16).

This agent, when used together with 5% palladium on charcoal (17), reduced ethylenic bonds under mild conditions, with evolution of nitrogen. Direct exchange of hydrogen at the surface of the catalyst was suggested as the mechanism. Maleic acid was converted to succinic acid (95% yield) and sorbic, muconic, and cinnamic acids were similarly reduced to the saturated acids.

A combination of Raney nickel and hydrazine hydrate was effective (18) in the conversion of aromatic nitro compounds to such amines as



Siloxene—Siloxene, $Si_6O_3H_6$, a silicon-containing polymer, was observed (19) to reduce aldehydes and ketones to the corresponding alcohols *via* intermediate, colored oxysiloxenes. In this manner, acetaldehyde, trichloroacetaldehyde, butyraldehyde, benzaldehyde, acetone, and acetophenone were converted to their corresponding alcohols.



Miscellaneous Chemical Reducing Agents—Aromatic nitro compounds have been reduced with powdered silicon (20) in ethanol or aqueous alkali to azo, azoxy, hydrazo, and amino derivatives. Mercaptans, e.g., *n*-octyl- and benzyl-, were recently desulfurized (21) with trialkyl phosphites to the corresponding hydrocarbons as shown. *p*-Thiocresol (22) and benzyl alcohol–potassium hydroxide (23) have been utilized, respectively, for saturation of exocyclic olefinic bonds in benzalquinaldine and cinnamylfluorene.

$$CH_3(CH_2)_7SH + (C_2H_5O)_3P \longrightarrow n\text{-octane} + (C_2H_5O)_3PS$$

Catalytic Reductions

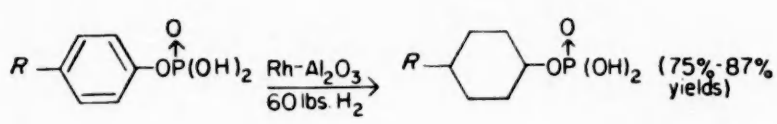
Hydrogen Transfer—Hydrogen transfer, with palladium as catalyst and cyclohexene as the hydrogen donor (by disproportionation to benzene), was discovered by Braude (24). This reaction is remarkably selective for the reduction of acetylenic and olefinic bonds and nitro-, azo-, azoxy-, azomethine-, and some halogen-containing compounds. Other functional groups, such as nitrile, carboxy, methoxy, hydroxy, and carbonyl (except in quinones and α-diketones) remain unchanged. Tetrahydrofuran is often used as the solvent in these reactions. Palladium is equally effective in colloidal form or when deposited on carbon, calcium carbonate, or alumina. In this manner, maleic acid, tolan ($C_6H_5C{\equiv}CC_6H_5$), and *p*-nitroacetophenone were quantitatively converted to succinic acid, dibenzyl, and *p*-aminoacetophenone, respectively.

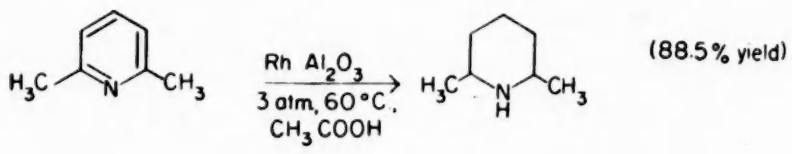
Modified Palladium Catalysts—Palladium–barium sulfate–quinoline was proved effective (25) as a highly specific catalyst for *cis*-reduction of acetylenic derivatives to olefins, and was found superior to Lindlar's catalyst (Pd-$CaCO_3$- poisoned with lead acetate and quinoline) in the reduction of dimethyl 5-decynedioate. Palladium

$$\begin{array}{l} C-(CH_2)_3COOCH_3 \\ \| \\ C-(CH_2)_3COOCH_3 \end{array}$$

on strontium carbonate or carbon carriers, used along with small amounts of alkali, is a comparatively recent innovation utilized successfully for the stereo-selective reduction of many steroid intermediates (26).

Rhodium on Alumina—Rhodium (5%) on alumina was utilized (27) for reduction of the benzene ring in aryl phosphonic acids to cyclohexyl derivatives. It has also been used for *cis*- reduction (28) of the N-heterocyclic, 2,6-lutidine.





Ruthenium Dioxide and Ruthenium on Carbon—Ruthenium dioxide, RuO_2, and ruthenium on carbon were used (29) to reduce carboxylic acids to the corresponding alcohols at a lower temperature (150°, 500-900 atm.) than can be effected with copper or cobalt catalysts. Acetic, succinic, oxalic, and hydroxyacetic acids were reduced by this method.

Platinum Oxide on Silicic Acid—Platinum oxide, PtO_2, supported on silicic acid, was shown (30) to be more stable and 2.5 times more active than Adams catalyst in the reduction of long-chain, unsaturated fatty esters. This new catalyst gave reproducible rate data and a sharper end-point in the reduction.

New Nickel–Zinc Catalyst—A more active nickel catalyst was prepared (31) by reaction of $NiCl_2 \cdot 6H_2O$ with zinc dust in hot water, followed by digestion with alkali at 50°-60° C. This catalyst, which consists of nickel and zinc in a ratio of 1:4.7, was successfully used at ordinary temperature and pressure for reduction of ketones, nitriles, oximes, and double bonds in conjugation with ketone or carboxyl groups.

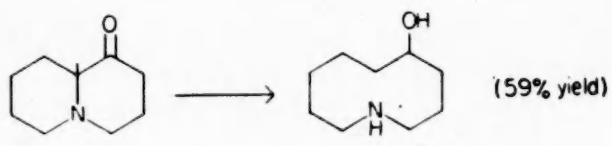
Electrolytic Methods

Electrolytic reduction of phthalic acid in a continuous mercury cathode has been recently introduced (32) as a synthetic approach to preparing the commercially valuable dihydrophthalic acid. This method possesses an advantage over the lead cathode procedure which has a rapid tendency to become inactivated by poisoning.

A 1,4-dihydrobenzene ring derivative was prepared (95% yield) from 2,7,8-trimethoxy naphthalene with a mercury cathode and tetra-*n*-butylammonium iodide in dioxane–water as catholyte and anolyte (33). This represented one of the first practical electrolytic reductions of a polynuclear carbocyclic aromatic system.

A method (34) was devised for anodic reduction of benzophenone and its derivatives to pinacols in a divided cell containing magnesium electrodes immersed in pyridine saturated with sodium iodide. Unipositive magnesium was indicated as the active reducing agent.

Finally, a unique method was developed (35) for the synthesis of medium-sized, monocyclic rings containing a nitrogen atom by electrolysis of bicyclic aminoketones at a lead cathode in 30% sulfuric acid. Facile scission of the C_α-N bond occurred in this process.



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